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Short Communication

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Birkitt-Linn Ten Tusscher, Stephen Trzeciak, Paul W. G. Elbers

B.-L. Ten Tusscher, P. W. G. Elbers (✉) Department of Intensive Care Medicine, VU University Medical Center, De Boelelaan 1117, 1081 HZ Amsterdam, The Netherlands, Tel: +31 20 / 44 44444, Fax: +31 20 / 44 44645, p.elbers@vumc.nl
S. Trzeciak Department of Emergency Medicine and Critical Care Medicine, UMDNJ-Robert Wood Johnson Medical School at Camden, Cooper University Hospital, Camden, USA

Introduction and background

In the last decade it is more and more recognized that in critically ill septic patients early resuscitation is crucial. Despite the introduction of treatment guidelines mortality of severe sepsis and septic shock remains high. The focus so far has been mainly on macrocirculatory goals. Dr. Trzeciak discusses the importance of the microcirculation for tissue perfusion, the disturbances of the microcirculation seen in sepsis and possible therapeutic strategies.

Methods

Analysis of dr. Stephen Trzeciak's presentation at the Frontiers in Critical Care congress on the 12th of April 2013 in Amsterdam, The Netherlands complemented by a review of relevant papers.

Results and main message

At the Frontiers in Critical Care congress in Amsterdam, Stephen Trzeciak held a lecture about the microcirculation, its role in sepsis and possible implications for resuscitation goals. Severe sepsis and septic shock have a high mortality rate and the best chance of increasing survival is optimization of treatment as early as possible. The Surviving Sepsis Campaign (SSC) guidelines recommend protocol--driven treatment of patients with severe sepsis and septic shock with targets of predefined physiological or laboratory goals to be achieved in the first ours of treatment in the emergency department [8].

Although the optimal goals of resuscitation are uncertain and highly debated, a meta-analysis did indicate a survival benefit if an early and quantitative resuscitation strategy is used in a heterogeneous population of septic patients [5]. The SSC guidelines recommend the use of central venous oxygen saturation ($ScvO_2$) or mixed venous oxygen saturation, this requires specific catheters with the possibility of complicating or delaying adequate treatment. A resuscitation strategy which uses lactate decrease instead of venous oxygenation as a marker of adequate tissue oxygen delivery and endpoint of adequate resuscitation appears to be at least equally effective and more practical [6].

However normalization of marcocirculatory parameters does not exclude persistence of microcirculatory disturbances with ongoing impaired tissue perfusion. Nowadays direct visualization of the microcirculation in tissues covered by a thin epithelial is possible with orthogonal polarization spectral (OPS) or sidestream dark field (SDF) imaging techniques [4].

Studies using these techniques demonstrated a grossly disturbed microcirculation in septic patients marked by a heterogeneity of blood flow with hyperperfused and hypoperfused capillaries in close vicinity to each other and a decreased functional capillary density ultimately causing tissue hypoxia in areas where capillary flow is insufficient [2].

Microcirculatory failure in sepsis results from increased aggregation and endothelial cell adherence of neutrophils, increased microvascular permeability, microvascular thrombosis, endothelial activation and dysfunction, and functional shunting [11]. The severity of microcirculatory changes in sepsis and the persistence these disturbances are both related to organ failure and death [9]. Therefore a goal-directed resuscitation protocol that focuses on macrocirculatory parameters alone may not be sufficient to optimize blood flow to tissues; ideally the microcirculation should also be targeted.

Under normal conditions nitric oxide (NO) plays an important role in regulation of microcirculatory homeostasis by regulating microvascular tone, leucocyte adhesion, platelet aggregation, microthrombi formation and microvascular permeability [7]. In sepsis systemic NO production is sharply increased, contributing to shock by refractory vasodilatation. Regional differences in NO availability, caused by both regional differences in inducible nitric oxide synthase (iNOS) expression and differences in NO consumption by reactive oxygen species, can cause areas with relative NO deficiency. Lack of NO availability can cause microcirculatory shunting, making NO an attractive candidate to treat microcirculatory dysfunction in sepsis [12].

A small clinical study of 8 septic patients showed promising results of improved microvascular flow with infusion of nitroglycerin after initial resuscitation [10]. A double blind randomized placebo controlled trial in a larger group of septic patients could however not demonstrate any improvement of microvascular flow in the nitroglycerin treated group versus the placebo group [1].

Dr. Trzeciak discussed his recently completed randomized trial of inhaled NO to augment the microcirculation perfusion in sepsis. The hypothesis of this trail was that NO can improve microcirculatory flow with the presumable benefit of a low risk of inducing or exacerbating arterial hypotension compared to infused nitroglycerin. After meeting quantitative resuscitation goals patients were randomized to treatment with inhaled NO or sham inhaled NO. Change in microcirculatory flow index from 0 to 2 hours was not statistically different between the 2 groups.

In a sheep model of peritonitis-induced septic shock supplementation of tetrahydrobiopterin (BH4) was studied. BH4 is a molecule that acts as an essential cofactor for the activity of NOS, particularly the endothelial NOS, and could possibly restore NO balance in sepsis. This study found substantial effects of BH4 on sublingual microcirculation and prolongation of survival [3]. However the microcirculatory alterations at baseline in these sheep were more severe than normally seen in septic patients and first dose of BH4 was administrated only 4 hours after sepsis induction. The question is if the positive effect on microcirculation and outcome can be repeated in clinical trials in patients with less severe disturbances of the microcirculation and administration later on in sepsis.

To further improve survival of severe sepsis and septic shock patients augmenting the microcirculation with addition of microcirculatory goals to the SSC guidelines seems a logical next step. So far however effective therapeutic agents are not available. The previousely mentiond study in sheep showed a promising new treatment option but further studies are needed.

Discussion

In the treatment of critically ill septic patients there is a limited window of opportunity and resuscitation should start as early as possible for optimal survival chances. The end goal of resuscitation should be restoration of perfusion to vital organs, and a functional microcirculation is a critical component necessary for effective blood flow to tissues. The early goal directed therapy of the Surviving Sepsis Campaign now mainly focuses the early treatment of septic patients on macrocirculatory goals. However restoration of macrocirculatory parameters does not exclude persistent disturbed microcirculation. More pronounced microcirculatory alterations and the persistence of these alterations are correlated with organ failure and death even if macrocirculation seems adequate. A focus not only on macrocirculatory goals but also microcirculatory parameters seem logical, with NO donors as potential therapeutic agents and further improvement of survival of sepsis patients may be dependent of microcirculatory recovery. Disturbed microcirculation in sepsis has now extensively been documented. The next step should be to target the microcirculation. Clinical studies with infused or inhaled NO agents in septic patients and other therapies aimed at recruiting the microcirculation with the purpose of restoring tissue perfusion and oxygenation have however so far been disappointing. A recent study of a NO synthase cofactor showed promising results in a sheep model of septic shock.

Conclusion

To improve outcome in critically ill septic patients early resuscitation is essential. Reaching macrocirculatory goals does not exclude persistence of microcirculatory disturbances with a negative effect on outcome.

Key messages

Early resuscitation in septic patients should ideally not only restore macrocirculation but also improve the microcirculation in order to restore tissue oxygenation.

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